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10/812,776	03/29/2004	David F. Muir	AXO-003C1	4996

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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,776	MUIR, DAVID F.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-23,30-40,42-56 and 117-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-23, 30-40, 42-56 and 117-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 6-23, 30-40, 42-56 and 117-123 as amended (11/12/2007) are pending and under examination.

Claims 2-5, 24-29, 41 and 57-116 are canceled by applicant.

Claim Rejections - 35 USC § 112

Claims 1, 6-23, 30-40, 42-56 and 117-123 as amended remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 38 recite a method for preparing a nerve graft with a first step of "degrading, by *in vitro* culturing, chondroitin sulfate proteoglycan of a nerve graft", thereby "enhancing post-implantation". The limitations such as "degrading CSPG" and "enhancing post-implantation" are the intended effects of "*in vitro* culturing" as claimed. The culturing step is generic as claimed. No treatment agents and/or conditions are recited in the claims. Thus, it is uncertain what "degrading" and/or "enhancing" treatments are encompassed in the method for preparing a nerve graft.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 6-15, 17-21, 30-40, 42-51, 53-56 and 117-120, 122 and 123 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by La Fleur et al. (IDS reference; J. Exp. Med. 1996, 184:2311-2326) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein method comprises 1) step of culturing the nerve tissue segment *in vitro* and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and DMEM medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue.

The reference by La Fleur et al. discloses a method for treating mammalian nerve tissue wherein method comprises 1) step of "culturing" the nerve tissue in vitro in DMEM medium comprising various supplements at temperature 37°C for various periods of time including 12, 24 and 2) step of "killing" the nerve tissue by chemical treatment for further extraction of proteins, RNA and other components (page 2312, column 2, par. 1-2). The nerve tissues or nerve segments are held or adhered to plastic dishes and, thus, combined with a generic adhesive. The nerve tissues derived from sciatic nerves that connected to both central and peripheral nervous system tissues.

The cited reference comprises identical active steps of culturing and killing nerve tissues under conditions as presently claimed. Thus, the cited reference anticipates the claimed invention.

2. Claims 1, 6-15, 17-23, 30-40, 42-56 and 117-123 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Lassner et al. (IDS reference; J. Reconstruct. Microsurg. 1995, 11 (6): 447-453) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue *in vitro* and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and DMEM medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by freezing. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays in vitro and in vivo.

The reference by Lassner et al. discloses a method for preparing a nerve tissue for use as a nerve graft wherein method comprises 1) step of culturing the nerve tissue segments *in vitro* under culture conditions including temperature permissive for cellular outgrowth or 37°C, time 48 hours and DMEM medium with serum, and 2) step of killing the nerve tissue by freezing at minus 18°C; for example: see page 448, column 2, last paragraph that relates to the second series of experiments. The nerve tissues or nerve segments are held or adhered to plastic dishes and, thus, combined with a generic adhesive. The nerve tissues derived from sciatic nerves that connected to both central and peripheral nervous system tissues. The cited reference also describes neurite outgrowth assays *in vitro* (figures 5 and 7) and *in vivo* regeneration upon reimplantation (page 449, col. 1).

The cited reference comprises identical active steps of culturing and killing nerve tissues under conditions as presently claimed. Thus, the cited reference anticipates the claimed invention.

3. Claims 1, 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 119, 122 and 123 as amended remain/are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,448,076 (Dennis et al) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue *in vitro* and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and a medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays in vitro and in vivo.

US 6,448,076 discloses a method for preparing a nerve tissue for use as a nerve graft (entire document including abstract) wherein the method comprises step of culturing *in vitro* the nerve graft in a medium or in a balanced salt solution (col. 3, lines 45-46), step of rendering the nerve graft acellular by chemical treatment (col. 3, lines 47-67 and col. 4, lines 26). The nerve graft is a mammalian peripheral nerve segment (col. 3, line 42). The cited patent discloses the 24-96 hours as time intervals for culturing/treating steps and the same temperature ranges including room temperature as required by the presently claimed method. Thus, the cited patent US 6,448,076 appears to teach the same active steps and the same structural elements in the

method of making graft as claimed. The acellular nerve grafts were used to repair nerve gap in vivo (col. 4, lines 47-60) and results were evaluated in vitro (col. 5, lines 53-66). The cited patent US 6,448,076 teaches that the nerve graft made supported axonal regeneration and allowed for end-organ reinnervation (col. 6, line 21-24) and, thus, enhanced post-implantation traversal of an interface between the nerve graft and host tissue within the meaning of the claims.

Therefore, US 6,448,076 anticipates the presently claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-23, 30-40, 42-56 and 117-123 as amended remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,448,076 (Dennis et al), La Fleur et al. (IDS reference; J. Exp. Med. 1996, 184:2311-2326), Ide et al. (IDS reference; "Schwann cell basal lamina and nerve regeneration". Brain Research. 1983, 288:61-75) and Evans et al. (IDS reference; Progress in Neurobiology, 1994. Vol. 43, pages 187-233) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue *in vitro* and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature

10°C to 37°C and a medium. Some claims are further drawn to the nerve tissues being mammalian including rodent and human. Some claims are further drawn to step of killing by freezing or by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays in vitro and in vivo.

US 6,448,076 (Dennis et al) is relied upon for disclosure of a method for preparing a nerve tissue graft as intended for implantation (entire document including abstract) wherein the method encompasses steps of *in vitro* culturing and/or *in vitro* treating the nerve graft and step of rendering the nerve graft acellular by killing.

In particular, the cited patent US 6,448,076 (Dennis et al) discloses a chemical treatment for making acellular nerve grafts and lacks explicit teaching about rendering nerve graft acellular through killing by freezing. However, Evans et al. teaches freezing and thawing of nerve grafts for making the nerve grafts acellular and non-immunogenic (page 212. col. 2, last par.). The cited reference by Ide et al teaches that basal laminae of Schwann cells rather than living cells play important role in nerve regeneration after implantation of nerve graft (page 62, col. 1, par. 1).

The cited patent US 6,448,076 (Dennis et al) teaches the use of balanced salt solution and Dubelco's modified base solutions for graft pre-treatment before acellularization but it lacks an explicit teaching about the use of an enriched culture media. However, La Fleur reference teaches that incubation of nerve segments in culture medium supplemented with cytokines results in up regulation of TIMP-1 expression and that TIMP-1 protects basement membrane of nerve tissue from uncontrolled disintegration or degradation after injury (abstract).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute a supplemented culture medium for a buffered salt solution in two-step method of US 6,448,076 (Dennis et al) with a reasonable expectation in success in making nerve tissues as intended for nerve grafts because culturing nerve tissues promotes up-regulation of compounds that remodel basement membrane of nerve tissues and protect from uncontrolled degradation after injury as adequately taught by La Fleur et al.

One of skill in the art would have been motivated to kill the nerve graft living tissues in order to avoid tissue rejection upon transplantation as clearly taught by Evans et al. Killing by chemical treatment and killing by freezing are considered to be substitution of equivalents.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 11/12/2007 have been fully considered but they are not found persuasive.

1. With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by **La Fleur et al**. applicants argue that the cited reference relates to effects that are essentially opposite of the claimed invention since the claimed method recites a degradation of GSPG by "culturing" a nerve segment but La Fleur teaches that TIMP-1 (inhibitor of MMP) protects basement membrane from MMP during degeneration (response pages 8-10). Arguments are not found

persuasive because the cited reference discloses method for making a nerve tissue segment or nerve tissue graft that comprises identical active steps such as 1) step of generic "culturing" a nerve tissue segment *in vitro* and 2) step of killing the nerve tissue. The claimed culture conditions are either generic (claim 1) or the claimed culture conditions including temperature, time and medium (claim 38, for example) are the same as recited for a culturing step in the cited reference. Thus, the intended final effects including "degrading CSPG" and "enhancing post-implantation" for remodeling/modifying nerve tissue segments cultured in vitro would be the same due to the use of identical "culturing" conditions. Moreover, the cited reference clearly acknowledges MMP as an inherent mediator of degradation of ECM components (page 2312, par. 2, for example) and it teaches that both MMP and its inhibitor TIMP are involved in remodeling nerve tissues.

Applicant also argues that the method as disclosed by La Fleur et al. is not intended for making a nerve graft suitable for implantation because the disclosed final step involves the use of Trizol solution that contains phenol and, thus, that is toxic and could cause necrosis, coma and death (response pages 10-11). Yet, the final step of the claimed method involves "killing" cells (claims 1 and 38) including "killing" by generic "chemical treatment" (claims 21 and 49, for example).

2. With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by **Lassner et al**. applicants argue (response page 11-13) that the method of the cited reference involved a cold storage at 4 degree C that is not a physiological conditions promoting degradation of CSPG. Yet, the rejected claims do not recite any specific culturing conditions

that lead to the intended effects such as promoting degradation of CSPG. Moreover, the cited reference also discloses some experiments that involve steps of "culturing" in DMEM or under physiological conditions and subsequent freezing as explained above. Applicants appear to argue that the second series of experiments disclosed by Lassner are intended for histological evaluation and involve the use of a toxic compound such as methanol. Yet, the final step of the claimed method involves "killing" cells (claims 1 and 38) including "killing" by generic "chemical treatment" (claims 21 and 49, for example). Thus, the active steps are identical as required by the claimed method and the culture conditions are the same within the broadest reasonable meaning of the claims.

3. With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 6,448,076 (**Dennis et al**) applicants argue (response pages 13-17) that Dennis does not recite the presently claimed effects including "degrading CSPG" and "enhancing post-implantation" and it rather relates to preservation of basal lamina. Yet, the final effects with regard to remodeling nerve tissue segment in vitro are considered to be the same as result of the same active steps of "in vitro culturing". The claimed "in vitro culturing" is either generic (claim 1) or the claimed "in vitro culturing" encompasses the same temperature, time and medium (claim 38, for example) as in the cited patent.

Applicant also argues that the method as disclosed by US 6,448,076 (Dennis et al) involve the use of Triton X-100 that is found to be damaging to basal laminae to at least some degree as evidenced by the reference by Hudson et al. (2004, IDS reference filed on 11/2007) at page 1356 column 2, first paragraph and, therefore, the nerve grafts made by the method of US

6,448,076 (Dennis et al) comprising treatment with Triton X-100 would not have "intact basal lamina tube structure" as encompassed by the instant claims. This argument is not found particularly convincing because the claimed term "intact basal lamina tube structure" appears to refer to preservation of a tubular structure and the images presented by the reference by Sondell demonstrate preserved tubular structure or preserved basal lamina tubes of the nerve segments treated with Triton X-100, for example: see Fig. 1 and Fig. 5 in the reference by Sondell et al. (1998, IDS filed on 11/12/2007).

In response to applicant's argument it is also noted that a recitation of the intended use or effects of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the instant case, the nerve grafts made by the cited method as disclosed by US 6,448,076 (Dennis et al) were implanted and provided for axonal regeneration post implantation (col. 6, line 24).

4. With regard to the claim rejection under 35 U.S.C. 103 applicants appear argue (pages 17-18) that there is no suggestion to combine cited references. However, the cited references are in the same field of endeavor such as method of making nerve grafts intended for repairing nerve damage in vivo and they seek to solve the same problems as the instant application and claims such as provide for nerve grafts intended for nerve damage repair in vivo, and one of skill in the art is free to select components available in the prior art, *In re* Winslow, 151 USPQ 48 (CCPA, 1966).

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova
AU 1657
January 29, 2008

VERA AFREMOVA
PRIMARY EXAMINER